"Synthesis and Characterization of Novel Polymorphs of Pharmaceutical Active Compound by Using Advance Technique"

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IN

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By

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Ph.D. Synopsis

Subject: Chemistry

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Introduction of Proposed Research:-

Pharmaceutical solids may be in the form of crystals and amorphous, crystal solvates or hydrates, crystal desolvated solvates or dehydrated hydrates, or amorphous solids. [1, 2] All crystal forms described can exist in different forms called polymorphs.

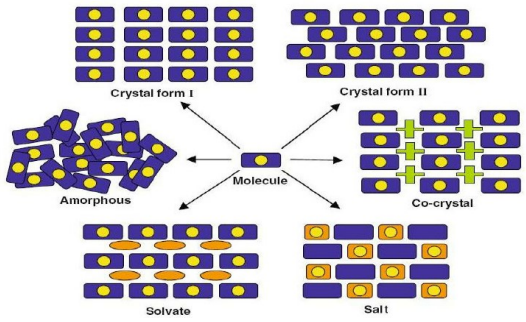


Fig: Types of Polymorphs

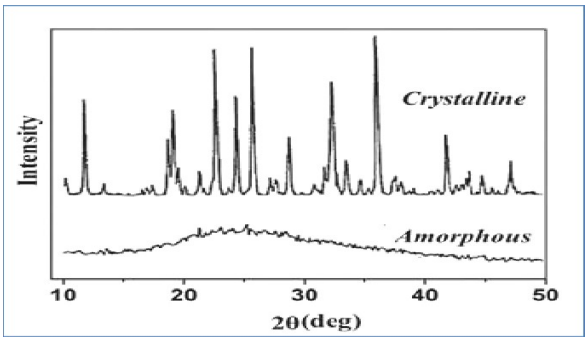
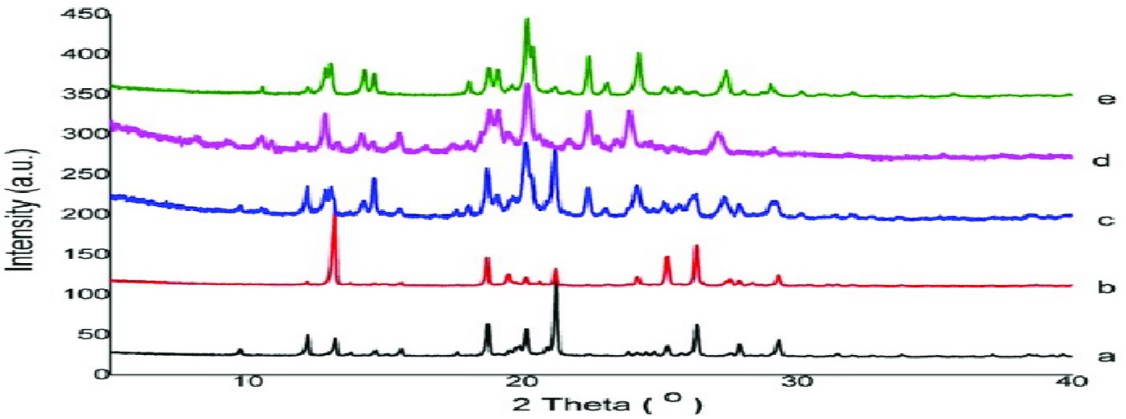


Fig: Crystalline and amorphous compound Diffractogram

The term polymorphism has been derived from the Greek word “poly”, which means “many”, and “morph” “implying “form”. Hence, polymorphism refers to different structural forms of a chemical substance. [3, 4]. CEO of GlaxoSmithKline said that “About 50 % of drug candidates that enter clinical trials fail due to efficacy and safety concerns, and the remaining 40% fizzle due to patent concerns and issues like solubility and drug interaction.” [5], [6] It is defined as the ability of a solid material to exist in two or more crystalline forms with different arrangements or conformations in the crystal lattice.[7] Polymorphs can have significant differences in their physical properties even though they are chemically identical. More than 50% of active pharmaceutical ingredients (APIs) are estimated to have more than one polymorphic form reported [8, 9]. Polymorphism and pseudomorphism are very common amongst drugs and are responsible for differences in many properties [10.]. Generally, polymorphism is considered to be of two types, viz. monotonic systems, and enantiotropic systems. [11-13] .In the former type, only one

polymorphic form is stable at temperatures below the melting point of the solid drug. However, in the latter, no such phenomenon is observed, though different forms can be more stable than the others irrespective of any noticeable temperature pattern. [14-16]

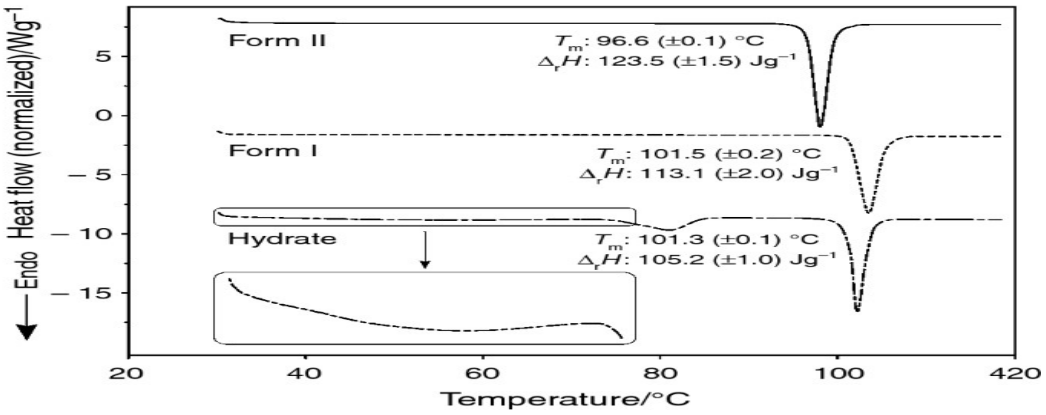


The significance of polymorphism in the pharmaceutical, pigment, electrical industry is mainly due to reasons. The first one is because the existence of polymorphism is inevitable. In other words, [17, 18,] polymorphism unavoidably occurs during the discovery, development, and/or manufacturing process. As Ostwald stated in 1899, “Almost every substance can exist in two or more solid phases provided the experimental conditions are suitable.”[19- 23]

Improvements in physicochemical properties can be achieved by altering the physical forms of a given compound such as polymorphs, solvates, amorphous, salts, cocrystals, and hydrates, etc. [24,25] Signal et al. Jean-Paul Garnier, CEO of GlaxoSmithKline said that “About 50 % of drug candidates that enter clinical trials fail due to efficacy and safety concerns, and the remaining 40% fizzle due to patent concerns and issues like solubility and drug interaction.” [26, 27,]. The physicochemical properties can be altered by preparing different polymorphs. The most important properties during drug discovery and development include solubility, dissolution, bioavailability, and physical/chemical stability. [29] An example is chloramphenicol palmitate (CAP), with polymorphs A and B. While A is the

thermodynamically stable form, it is therapeutically inactive. Form B is a higher energy form, so it dissolves more easily in water, raising its bioavailability [30–31]. Aguiar et. al. showed that the peak blood serum level of CAP increases linearly as the percentage of form B is increased from ~3 μg/mL (for all form A) to 22 μg/mL (for 100% f). Identification of the polymorphic form of an Active Pharmaceutical Ingredient (API) is of critical importance when dealing with APIs prone to changing crystal structure during the life cycle of the pharmaceutical product. [32-34] Crystal identification of active pharmaceutical ingredients via advanced analysis, including XRPD, DSC, FTIR, and, to determine the best polymorphic form for your product. [35],

For the compounds exhibiting polymorphism, the knowledge of the thermodynamic stability and thermo kinetics is desired for a better understanding of the transformations and the time span required for these transformations [36]. The existence of two basic polymorphic forms, viz. monotropes and enantiotropic is assumed on these bases The relative stability and driving force for the polymorphic transformations at constant temperature and pressure is determined by Gibbs free energy (ΔG); the internal energy available for chemical work, as portrayed by equation 1: $\Delta G = \Delta H - T \Delta S$ (1) Where ΔH signifies the enthalpy change, while ΔS accounts for the entropy change. A negative value of ΔG assures the spontaneity of the polymorphic transitions, whereas the positive value renders the process non-spontaneous. [37-41] XRD followed by DSC is the gold standard for crystal structure analysis. The diffraction pattern gives a unique fingerprint of the crystal structure. [42]



Literature Review of the Proposed Topic:

The development of novel polymorph of drug substances to facilitate the preparation of desired Molecules is an intense area of research. In this regard, efforts will be made to get novel polymorph of different drugs and a new analytical methodology will be introduced to characterize novel polymorphs like X-ray diffraction, DSC, TGA, Image analysis, etc.

Gaps in Existing Research:-

From the Literature review, it is clear that more work in the field of polymorphism was carried out post-WTO treaty 2005. [43,44] However drug molecules prior to that of the treaty were not much studied for polymorphism such drug will be studied in the research for the preparation of possible polymorph and also drug where polymorphism is reported, still, there is a chance of preparation of novel polymorphs, Hence such drug can also study for synthesis new polymorph.

It is of great interest challenges for researchers all over the world to design and develop new polymorph of active phramasctical ingredient methodologies for the synthesis of a polymorph of APIs. There are very few analytical methodologies are available for the determination of polymorph content in another polymorph of an active pharmaceutical compound. [45, 46]

Statement of Proposed Problem:-

1. Novel polymorph of compounds have great importance due to biological availability Associated with them. Polymorph of drug substance has wide application in phramasctical filed and having industrial significance hence preparation of novel polymorph is challenging Task.

2. There are very few analytical methods and techniques are available in the crystallography field.

3. Advance techniques like XRD, DSC, TGA, and its interlinked study for the novel polymorphism is cripolymorphism nature.

Scope of Research Work:-

This research will provide great insight into the polymorph future for the researchers and Pharmaceutical industries to develop new procedures which. It will help to the development of novel polymorph which is having good Bioavailability one the important.

Relevance of the Research Work:-

In recent times, the progress in the field of developing novel polymorphs is gaining Significance because of their high efficiency, bioavailability, and intern lower dose of the drug product.

Significance of the study:

This research will provide a great alternative in the future for the researchers and Phramasctical industries to develop new procedures which are eco-friendly benign. A novel polymorph with to achieve the goal of higher bioavailability and subsequently lower dose.

Objectives of the Research:

We are interested in seeking new processes to manufacture novel polymorphs of different drugs involving a variety of different methodologies.

1. To prepare Novel polymorphic forms of various active pharmaceutical ingredients.

2. To study the morphology of novel polymorphic forms using the microscopic technique.

3. To characterize newly prepared novel polymorphic forms using an advanced technique like XRD, DSC, IR, etc.

Hypothesis:

To get novel polymorphic forms of drugs substance different methods will be employed including single and multi-solvent crystallization, lyophilization, sublimation, spray drying, air drying at various temperatures, sublimation, grinding, slow cooling, etc. [47, 48,]. Polymorph characterization or screening will be done by Various techniques that have been used to characterize the polymorphs like thermal analysis differential scanning calorimetric DSC, Thermogravimetric analysis TGA, infrared FT-IR spectroscopy, Raman spectroscopy, powder X-ray diffraction XRD, single crystal XRD, solid-state NMR, terahertz spectroscopy, Thermal properties of polymorphs are an important aspect and are generally fetched by DSC and TGA [49-51]. FT-IR helps to identify the polymorphs by indicating changes in frequencies, relative intensities. The difference in spectra gives an inference to the internal arrangement of crystals [52-54]. Raman spectroscopy is analogous to FT-IR spectroscopy and is considered an ideal non-destructive tool for polymorphic studies.

Plan of work:

Plan work will be completed in Three Phases

Phase –I

In the First phase, the extensive Literature research and collection of references Literature Survey, final idea of the work, and preliminary synthesis of novel polymorphs

Phase II:

Synthesis of novel polymorphs and development of a new analytical method for determination of novel polymorphs by using XRD, DSC, IR, etc.

Phase III:

Polymorph Generation and reproducibility check of novel polymorph, Analytical Method of the compounds like IR, DSC, Image analysis, XRD method development, publishing of the work, and Thesis writing.

The work carried out under this scheme will be submitted in the form of a thesis for the award of a Ph.D. degree in chemistry.

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